SYNTHESIS OF 1-SUBSTITUTED ISOQUINOLINES; N-ACYLATION, PHOSPHONATION, WITIG REACTION, MORPHINE INTERMEDIATES

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Abstract:

A method for the synthesis of particular isoquinoline compounds which are useful intermediates in the preparation of members of the family of opium alkaloids , such as morphine and codeine . Steps in the process include the acylation of the isoquinoline nitrogen; reaction of the acylated isoquinoline with a phosphorous compound; and condensation with a benzaldehyde derivative to yield a 1-benzyl isoquinoline.

Exemplary Claim:

1. A METHOD OF PREPARING A MORPHINE INTERMEDIATE OF THE FOLLOWING FORMULA (I):

1-((3-X,4-Y,5-Z,6-Z1-PHENYL)-HC=),2-R1,6-R2-1,2-DIHYDROISOQUINOLINE (I)

WHEREIN R1 IS COR GROUP WHEREIN R IS C1-6 ALKYL, PHENYL, OR C1-6 ALKOXY; R2 IS HYDROGEN OR C1-6 ALKOXY; X AND Z, WHICH MAY BE THE SAME OR DIFFERENT, ARE HYDROGEN, HYDROXY, SILYLOXY, HALOGEN, LOWER ALKOXY, PHENOXY, LOWER ALKYL, TRIMETHYLSILOXY, PHENYL, OR BENZYLOXY; Y IS HYDROXY, SILYLOXY, HALOGEN, LOWER ALKOXY, PHENOXY, PHENYL, OR LOWER ALKYL; Z1 HYDROGEN OR HALOGEN, COMPRISING THE FOLLOWING STEPS (I) REACTING AN ISOQUINOLINE OF THE FOLLOWING FORMULA (II):

6-R2-ISOQUINOLINE (II)

WHEREIN R2 IS AS DEFINED ABOVE, WITH A COMPOUND OF THE FORMULA LG-R1, WHEREIN LG IS MERCAPTO, HYDROXY, HALOGENO, LOWER ALKOXY, OR LOWER ALKYLTHIO AND R1 IS AS DEFINED ABOVE, FOLLOWED BY (II) REACTING THE N-ACYLATED PRODUCE OF STEP (I) WITH A PHOSPHORUS COMPOUND CAPABLE OF BEING DISPLACED FROM THE COMPOUND OF THE FOLLOWING FORMULA (III) AS THE PHO MOIETY BY A WITTIG REACTION USING N-BUTYL LITHIUM AND ISOVANILLIN, TO YIELD A COMPOUND OF THE FOLLOWING FORMULA (III):

1-PHO,2-R1,6-R2-1,2-DIHYDROISOQUINOLINE (III)

WHEREIN PHO IS A PHOSPHONATE PO(OR)2 WHEREIN R IS LOWER ALKYL. R1 AND R2, ARE AS DEFINED ABOVE; AND (III) REACTING THE COMPOUND OF FORMULA (III) IN A WITTIG REACTION WITH THE BENZALDEHYDE OF THE FOLLOWING FORMULA (IV):

1-CHO,2-Z1,3-Z,4-Y,5-X-BENZENE

WHEREIN X, Y, Z, AND Z1 ARE AS DEFINED ABOVE, TO YIELD A COMPOUND OF FORMULA (I).